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US

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LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,  
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CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).**Published***With international search report.**Before the expiration of the time limit for amending the  
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amendments.*

(88) Date of publication of the international search report:

13 November 1997 (13.11.97)

(54) Title: METHODS OF TREATMENT WITH COMPOUNDS HAVING RAR<sub>α</sub> RECEPTOR SPECIFIC OR SELECTIVE ACTIVITY

## (57) Abstract

Retinoid compounds which act specifically or selectively on RAR<sub>α</sub> receptor subtypes in preference over RAR<sub>β</sub> and RAR<sub>γ</sub> receptor subtypes, possess desirable pharmaceutical properties associated with retinoids, and are particularly suitable for treatment of tumors, such as acute monocytic leukemia, cervical carcinoma, myeloma, ovarian carcinomas and head and neck carcinomas, without having one or more undesirable side effects of retinoids, such as inducement of weight loss, mucocutaneous toxicity, skin irritation and teratogenicity.

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/20511

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/19 A61K31/215 A61K31/34 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 93 03713 A (SALK INST FOR BIOLOGICAL STUDI) 4 March 1993</p> <p>see page 9, line 4 - line 31; claims 1-15</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>1-4, 6-12, 14-22</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*A\* document member of the same patent family

Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/US 96/20511

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 121, no. 9, 1994 Columbus, Ohio, US; abstract no. 108128d, XP002030814 see abstract & YU, BAOXIN ET AL: "Synthesis of p-substituted benzoylaminobenzoic acid (methyl esters) and its differentiation induction activities of human promyelocytic leukemia cells HL-60" HUAXI YIKE DAXUE XUEBAO, vol. 25, no. 1, 1994, pages 30-34, ----	1-4, 6-12, 14-22
Y	DATABASE WPI Section Ch, Week 9416 Derwent Publications Ltd., London, GB; Class B05, AN 94-128759 XP002030803 & JP 06 072 866 A (CHUGOKU IGAKUKAGAKUIN YAKUBUTSU KENKYUSH) , 15 March 1994 see abstract ----	1-4, 6-12, 14-22
Y	EP 0 514 269 A (CIRD GALDERMA) 19 November 1992  see page 3, line 3 - page 3, line 9; claims 1-21 especially claim 16, ex. 15 ----	1-4, 6-12, 14-22
Y	EP 0 350 846 A (HOFFMANN LA ROCHE) 17 January 1990  see page 5, line 43 - page 6, line 35; claims 1-18 ----	1-4, 6-12, 14-22
Y	US 5 420 145 A (SHUDO KOICHI) 30 May 1995  see column 3, line 65 - column 4, line 29; claims 1-4 ----	1-4, 6-12, 14-22
Y	EP 0 170 105 A (SHUDO KOICHI ;SUMITOMO PHARMA (JP); YOSHITOMI PHARMACEUTICAL (JP)) 5 February 1986 see claims 1-11 ----	1-4, 6-12, 14-22
P,Y	WO 96 32101 A (TAIHO PHARMACEUTICAL CO LTD ;SHIBATA JIRO (JP); WIERZBA KONSTANTY) 17 October 1996 see abstract ----	1-4, 6-12, 14-22

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/20511

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>KAGECHIKA H ET AL: "RETINO BENZOIC ACIDS STRUCTURE-ACTIVITY RELATIONSHIPS OF AROMATIC AMIDES WITH RETINOIDAL ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 11, November 1988, pages 2182-2192, XP000608417 see tables I-VI see page 2187, left-hand column, last paragraph - page 2188, left-hand column</p>	<p>1-4, 6-12, 14-22</p>
P,Y	<p>MIN TENG ET AL: "Identification of a Retinoic Acid Receptor alpha Subtype Specific Agonist" J. MED. CHEM., vol. 39, no. 16, 2 August 1996, pages 3035-3038, XP000652115 see the whole document</p>	<p>1-4, 6-12, 14-22</p>

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/20511

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See annex.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4, 6-12, 14-22 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 98 20511

FURTHER INFORMATION CONTINUED FROM PCT/ISA210

1. The use of a RAR alpha selective agonist for the prevention/treatment of acute monocytic leukemia, cervical carcinoma, myeloma, ovarian carcinomas, head and neck carcinomas (respective portions of Claims 1- 4, 6-12, 14 - 22)
2. The use of a RAR alpha selective agonist for the prevention/treatment of proliferative vitreoretinopathy (PVR), age related macular degeneration (AMD), diseases of the eye, retinal detachment, dry eye, other corneopathies (respective portions of Claims 1 - 22)
3. The use of a RAR alpha selective agonist for the prevention/treatment of actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses, eczema, atopic dermatitis, Darriers disease, lichen planus, skin pigmentation, age and photo damage to the skin, premalignant and malignant hyperproliferative diseases, Kaposi's sarcoma (respective portions of Claims 1, 2, 4 - 13, 15- 22)
4. The use of a RAR alpha selective agonist for the prevention/treatment of cardiovascular diseases (respective portions of Claims 1, 2, 4 - 13, 15- 22)
5. The use of a RAR alpha selective agonist for the prevention/treatment of dyslipidemias (respective portions of Claims 1, 2, 4 - 13, 15- 22)
6. The use of a RAR alpha selective agonist for the prevention of post-angioplasty restenosis (respective portions of Claims 1, 2, 4 - 13, 15- 22)

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96 20511

FURTHER INFORMATION CONTINUED FROM PCT/ISA210

7. The use of a RAR alpha selective agonist for the prevention/treatment of diseases associated with human papilloma virus (HPV) (respective portions of Claims 1, 2, 4 - 13, 15- 22)
8. The use of a RAR alpha selective agonist for the for the prevention/treatment of inflammatory diseases (respective portions of Claims 1, 2, 4 - 13, 15- 22)
9. The use of a RAR alpha selective agonist for the prevention/treatment of neurodegenerative diseases (respective portions of Claims 1, 2, 4 - 13, 15- 22)
10. The use of a RAR alpha selective agonist for the prevention/treatment of improper pituitary function (respective portions of Claims 1, 2, 4 - 13, 15- 22)
11. The use of a RAR alpha selective agonist for the prevention/treatment of insufficient hair growth (respective portions of Claims 1, 2, 4 - 13, 15- 22)
12. The use of a RAR alpha selective agonist for the prevention/treatment of diseases associated with the immune system (respective portions of Claims 1, 2, 4 - 13, 15- 22)
13. The use of a RAR alpha selective agonist for wound healing (respective portions of Claims 1, 2, 4 - 13, 15- 22)

The search has been limited to the subject-matter of item 1.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/20511

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9303713 A	04-03-93	AU 2516092 A CA 2114936 A EP 0600028 A JP 7505607 T US 5668175 A	16-03-93 04-03-93 08-06-94 22-06-95 16-09-97
EP 0514269 A	19-11-92	FR 2676440 A AT 129698 T AU 650972 B AU 1627392 A CA 2068696 A DE 69205725 D DE 69205725 T ES 2080458 T JP 5221951 A	20-11-92 15-11-95 07-07-94 19-11-92 16-11-92 07-12-95 30-05-96 01-02-96 31-08-93
EP 0350846 A	17-01-90	AT 128974 T AU 626881 B AU 3709789 A CA 1319364 A DE 58909463 D ES 2078905 T FI 96204 B IE 70450 B IL 90912 A JP 2053684 C JP 2076862 A JP 7086094 B PT 91158 B US 5420273 A US 5037825 A US 5164387 A US 5300522 A MX 16751 A	15-10-95 13-08-92 18-01-90 22-06-93 16-11-95 01-01-96 15-02-96 27-11-96 25-01-94 23-05-96 16-03-90 20-09-95 01-03-95 30-05-95 06-08-91 17-11-92 05-04-94 01-10-93
US 5420145 A	30-05-95	EP 0617020 A	28-09-94
EP 0170105 A	05-02-86	JP 1764534 C JP 4058458 B JP 61022047 A	28-05-93 17-09-92 30-01-86

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/20511

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0170105 A		JP 1764542 C	28-05-93
		JP 4058459 B	17-09-92
		JP 61076440 A	18-04-86
		US 4703110 A	27-10-87
<hr/>			
WO 9632101 A	17-10-96	AU 5287596 A	30-10-96
		CA 2191850 A	17-10-96
		EP 0768084 A	16-04-97
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